UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,157	10/15/2003	Bernard Knoops	DECLE30.001CP1	6185

20995 7590 10/12/2006

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,157	KNOOPS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-15* is/are pending in the application.

4a) Of the above claim(s) *7-11* is/are withdrawn from consideration.

5)☒ Claim(s) *5* is/are allowed.

6)☒ Claim(s) *4, 6 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4-15 are pending.

2. Claims 7-11 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. The following new grounds of objection and rejections are necessitated by the amendment filed 7/17/06.

4. The amendment filed 7/17/06 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "601884" in paragraph 0107. Applicant is required to cancel the new matter in the reply to this Office action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 4, 6 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a polypeptide comprising SEQ ID NO: 2 for treating ibotenate induced brain lesions, and (2) a peptide consisting of the amino acid sequence selected from the group consisting of the sequence between the glutamic acid in position 14 and the glutamic acid in position 28 of SEQ ID NO: 2, the alanine in position 27 and the leucine in position 37 of SEQ ID NO: 2, the alanine in position 43 and the glutamic acid in position 58 of SEQ ID NO: 2, the glutamic acid in position 57 and the valine in position 70 of SEQ ID NO: 2, the valine in position 81 and the leucine in position 97 of SEQ ID NO: 2, the arginine in position 96 and the leucine in position 112 of SEQ ID NO: 2, the serine in position 119 and the serine in position 130 of SEQ ID NO: 2, and the valine in position 138 and the threonine in position 151 of SEQ ID NO: 2, the glutamic acid in position 14 and the cysteine in position 48, the glutamic acid in position 14 and the glycine in position 39, the leucine in position 37 and the cysteine in

position 48 and the threonine in position 151 and the leucine in position 162 for diagnosing osteoarthritis cartilage or for making antibody, **does not** reasonably provide enablement for (1) any amino acid sequence "having more than 95% *homology*" with the sequence of SEQ ID NO: 2, 4 or 6 (2) any pharmaceutical formulation in an orally administrable dosage form, comprising any amino acid sequence "having more than 95% homology" with the sequence of SEQ ID NO: 2, or any pharmaceutically acceptable salt thereof or any derivative thereof, (3) any amino acid sequence "having more than 95% *homology*" with the sequence of SEQ ID NO: 2 produced in yeast, (4) any pharmaceutical formulation for treating human cerebral palsy, any neurodegenerative conditions associated with oxidative stress related to NMDA receptor mediated excitotoxicity and osteoarthritis, comprising any amino acid sequence "having more than 95% *homology*" with the sequence of SEQ ID NO: 2, any pharmaceutical acceptable salt thereof or any derivative thereof for treating any diseases as set forth in claim 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one human peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 for treating ibotenate induced brain lesions. The specification at page 39 paragraph 136 discloses intracerebral administration of recombinant peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 had no detectable protective effect on other neurotoxic injury or excitotoxic brain lesion induced by S-bromowillardiine. The specification further discloses peptide consisting of the amino acid sequence selected from the group consisting of the sequence between the glutamic acid in position 14 and the glutamic acid in position 28 of SEQ ID NO: 2, the alanine in position 27 and the leucine in position 37 of SEQ ID NO: 2, the alanine in position 43 and the glutamic acid in position 58 of SEQ ID NO: 2, the glutamic acid in position 57 and the valine in position 70 of SEQ ID NO: 2, the valine in position 81 and the leucine in position 97 of SEQ ID NO: 2,

the arginine in position 96 and the leucine in position 112 of SEQ ID NO: 2, the serine in position 119 and the serine in position 130 of SEQ ID NO: 2, and the valine in position 138 and the threonine in position 151 of SEQ ID NO: 2, the glutamic acid in position 14 and the cysteine in position 48, the glutamic acid in position 14 and the glycine in position 39, the leucine in position 37 and the cysteine in position 48 and the threonine in position 151 and the leucine in position 162 for making antibody.

The specification does not teach how to make any and all amino acid sequence mentioned above because there is insufficient guidance as to the structure without the amino acid sequence of any amino acid having merely more than 95% *homology* with the sequence of SEQ ID NO: 2 or any derivative of any amino acid having merely more than 95% *homology* with the sequence of SEQ ID NO: 2 for a pharmaceutical composition for treating any diseases such as the ones recited in claim 15.

The specification does not teach how to identify other amino acid sequence or variants of SEQ ID NO: 2 that has at least 5% amino acids difference, much less the function of such undisclosed amino acid sequence, in turn, would be effective for treating brain lesions or any excitotoxic injury caused by oxidative stress that affects neuronal cells or autoimmune osteoarthritis. The specification does not teach which amino acids within the full-length sequence of SEQ ID NO: 2 are critical and can or cannot be change such as substitution, deletion, addition and combination thereof and whether the variant or derivative still maintains its structure and function, in turn, would useful for treating excitotoxic brain lesion induced by S- ibotenate, let alone any neurotoxic injury or excitotoxic injury induced by any agent such as S-bromowillardiine. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo. There is no recognition in the art that sequence identity predicts biological function and therefore a disclosure of sequence identity does not lead one of skill in the art at the time the invention was made to believe said identity gives a credible use to the claimed protein. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) teach in activin A, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and loss of receptor binding activity (See

Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular).

Attwood *et al*, (PTO 892), teaches that protein function is context-dependent; the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable and knowing structure alone will not inherently tell us function (See figure, entire document).

Given the unlimited number of amino acid sequence, there is insufficient in vivo working example showing that any undisclosed amino acid sequences, particularly the derivative thereof and salt thereof of any amino acid sequence merely having more than 95% homology to SEQ ID NO: 2 are effective for treating all neurotoxic injury, any excitotoxic injury, any excitotoxic injury such as osteoarthritis. In fact, the specification at page 39 paragraph 136 discloses intracerebral administration of recombinant peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 had no detectable protective effect on other neurotoxic injury or excitotoxic brain lesion induced by S-bromowillardiine.

It is known that autoimmune osteoarthritis is model dependent. It is not clear the reliance of intracerebral administration to any mouse pup is the appropriate model for autoimmune osteoarthritis.

With regard to "derivative thereof", there is a lack of guidance as to which amino acids to within the full-length sequence of SEQ ID NO: 2 to be modified by addition, deletion, substitution or any combination thereof such the resulting derivative has biological function. The specification does not teach any of the fragment of SEQ ID NO: 2 has any activity in vitro or in vivo. There is not a single fragment from the smallest to the largest fragment shows any biological effect for treating any brain lesions caused by any neurotoxic injury or excitotoxic injury.

As such, treatment of neurotoxic injury or any excitotoxic injury or osteoarthritis using any undisclosed amino acid sequence of any homologoue of SEQ ID NO: 2 that has 95% sequence homology or derivative thereof is highly unpredictable, varies depending on the animal model, means of administration and composition of the polypeptide.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 7/17/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 1-3 have been canceled. Claim 4 has been amended to recite having at least 95% homology to SEQ ID NO: 2. The application discloses not only SEQ ID NO: 2, which relates to the human PRDX5 sequence, but also SEQ ID NOS: 4 and 6, which relate to the rat and mouse PRDX5 sequence, respectively. Notably, the mitochondrial targeting pre-sequence is missing from these sequences. Upon aligning SEQ ID NOS: 2, 4 and 6, 12 amino acids differed over a total 162 amino acids. This reflects an overall homology of about 93% between the three sequences and also provides guidance to one skilled in the art as to which residues may be modified with retention of activity. See also Figure 5 of the present specification which shows homology between the human and rat B18 (PRDX5) amino acid sequences as 97.5% and between the human and mouse B 18 (PRDX5) sequences as 96%. Accordingly, Applicants respectfully submit that the present specification is enabling for sequences having 95% homology as two additional sequences having more than 95% homology to SEQ ID NO: 2 are described in the present specification. Furthermore, an alignment of the three sequences provides sufficient guidance to one skilled in the art to determine which residues may be replaced or deleted without loss of biological activity.

Regarding Utility, the Examiner admits that SEQ ID NO: 2 has utility for treating ibotenate induced brain lesions and that the subsequences of claim 5 have utility for diagnosing osteoarthritis cartilage or making antibody (see item 10 on page 4 of paper no. 03032006). Furthermore, with respect to the fragments as claimed in claim 5, support for the asserted utility is disclosed in the present specification at paragraphs 0041-0046 which discloses use of peptide fragments to generate antibodies and their use in a diagnostic device such as a kit or column.

Regarding the utility of SEQ ID NO: 2, (claims 4, 6, and 12-15), the specification discloses at paragraph 0134 that "intraperit0neal administration of recombinant PRDX5 immediately after ibotenate produced a dose-dependent protection against the ibotenate-induced cortical plate and white matter lesions (Figures 10B and 11A)". Also, as disclosed in paragraph 0137, "tunel staining performed at 8 and 48 hours following ibotenate injection showed that recombinant PRDX5 induced a significant reduction of cortical plate [and white matter cell death] (Figure 12)". As discussed in paragraph 0138, when compared to control, exposure to PRDX5 induced a reduction of NMDA-induced neuronal cell death (Figure 13A) and co-treatment with PRDX5 and DTT induced a larger reduction of NMDA-induced cell death. In further support of the evidence provided by the present specification, Applicants' present two articles from peer reviewed journals which relate to the present application (see Attachment A). Plaisant, et al. "Recombinant Peroxiredoxin 5 protects Against Excitotoxic Brain Lesions in Newborn Mice" (2003) Free Radical Biology & Medicine, vol. 34, no.7: pages 862-872. Wang, et al. "Expression and Regulation of Peroxiredoxin 5 in Human Osteoarthritis" (2002) FEBS Letters vol. 531: pages 359-362.

The article by Plaisant, et al. describes data corresponding to the data presented in the present specification. The article by Wang, et al. provides evidence for a role for PRDX5 in osteoarthritis and concludes that "PRDX5...*may have* therapeutic value in the prevention and treatment of OA". Applicants would like to emphasize that the acceptance and publication of this data by peer reviewed journals underscores the scientific reliability and reproducibility of the present invention. Accordingly, Applicants respectfully submit that SEQ ID NO: 2, per se, and all of the subsequences of claim 5 as amended have a utility.

The Examiner cites Mason, et al. for their teaching that replacement of cysteine residues in activin A results in loss of activity. However, this reference does not relate to PRDX5 sequences. Mason, et al. is a specific teaching for activin A. At best, Mason, et al. may be pertinent to dimers linked by a disulfide bond. However, Mason, et al. is not pertinent here. Atwood, et al. cited by the examiner, relates to bioinformatics and not to the present case where a function may be assigned to a specific sequence. The present claims relate to a specified structure characterized by SEQ ID NO: 2, which has an experimentally proven function, in contrast to the computationally predicted functions of possible proteins of Atwood. Nevertheless, Atwood admits that function prediction through pattern recognition is possible (page 2, penultimate paragraph), contrasting the opinion by the examiner on page 6, line 6 et seq stating

that "There is no recognition in the art that sequence identity [sic.] predicts biological function and therefore a disclosure of sequence identity does not lead one of skill in the art at the time the invention was made to believe said identity gives a credible use to the claimed protein." Accordingly, neither Mason, et al. nor Atwood, et al. support the Examiner's position with respect to the present case. On page 7, first sentence, the Examiner states that "it is known that autoimmune osteoarthritis is model dependent" and implies that intracerebral administration to a mouse pup is an inappropriate model for autoimmune osteoarthritis. However, this statement is made without any supporting evidence and so may be set aside.

In response, enablement is not commensurate in scope with claims how to make any "analog" and any "homolog" that is 95% homologous to SEQ ID NO: 2 for treating any osteoarthritis, or any diseases such as the ones recited in claim 15.

The claims are drawn to any homologue that is 95% identical to SEQ ID NO: 2, any derivative of said homologue for treating any neurotoxic injury or any excitotoxic injury or osteoarthritis.

The specification discloses only one human peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 for treating ibotenate induced brain lesions. The specification at page 39 paragraph 136 discloses intracerebral administration of recombinant peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 had no detectable protective effect on other neurotoxic injury or excitotoxic brain lesion induced by S-bromowillardiine. The specification also discloses SEQ ID NOS: 4 and 6, which relate to the rat and mouse PRDX5 sequence, respectively. However, the functions of SEQ ID NO: 4 and 6 have not been disclosed.

The term "homology" as taught by Attwood et al is that the term "homology," a fundamental concept in bioinformatics, is often used incorrectly. Sequences are homologous if they are related by divergence from a common ancestor. Conversely, analogy relates to the acquisition of common structural or functional features via convergent evolution from unrelated ancestors. For example, 3barrels occur in soluble serine proteases and integral membrane porins, but despite their common architecture, they *share no sequence or functional similarity*. Similarly, the enzymes chymotrypsin and subtilisin share groups of catalytic residues with almost identical spatial geometries, but they have no other sequence or structural similarities. Homology is not a measure of similarity, but rather an absolute statement that sequences have a divergent rather than a convergent relationship (see paragraph bridging pages 2 and 3, in particular). Although the

specification discloses homologous sequence of SEQ ID NO: 4 and 6, the specification is silent the two sequence of SEQ ID NO: 4 and 6 perform the same functions as the human PRDX5 of SEQ ID NO: 2.

Further, the specification does not teach how to make any derivative of any amino acid sequence having more than 95% homology with SEQ ID NO: 2, much less for treating any neurotoxic injury or any excitotoxic injury or osteoarthritis. There is a lack of guidance as to which amino acids to within the full-length sequence of SEQ ID NO: 2 to be modified by addition, deletion, substitution or any combination thereof such the resulting derivative has biological function. The specification does not teach any of the fragment of SEQ ID NO: 2 has any activity in vitro or in vivo. There is not a single fragment from the smallest to the largest fragment shows any biological effect for treating any brain lesions caused by any neurotoxic injury or excitotoxic injury or osteoarthritis. As evidence by the teachings of Mason *et al* (of record, Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) that activin A, a homologue of transforming growth factor β, and also a member of the bone morphometric protein family that plays a role in osteoarthritis, where even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Given the unlimited number of derivative, the specification does not teach any assays that is predictable of in vivo success. The specification does not teach any of the fragment of SEQ ID NO: 2 has any activity in vitro or in vivo. There is not a single fragment from the smallest to the largest fragment shows any biological effect for treating any brain lesions caused by any neurotoxic injury or excitotoxic injury. In fact, the specification at page 39 paragraph 136 discloses intracerebral administration of recombinant peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 had no detectable protective effect *on other neurotoxic injury* or excitotoxic brain lesion induced by S-bromowillardiine.

With respect to the article by Wang et al, Wang et al teach peroxiredoxin 5 protein is expressed in human osteoarthritis cartilage as measured by Western blot analysis (see page 360, Figure 1, in particular). Wang et al teach inflammatory cytokine such as TNFα and IL-1 increased PRDX5 expression in human chondrocytes in vitro. However, at 48 hrs, the protein levels of PRDX5 returned to baseline levels (see Figure 2B and 3B, in particular). Wang et al

conclude that more experiments are necessary to define the translational regulation of PRDX5 protein in human chondrocytes (see page 360, first paragraph, in particular). Wang et al teach the functional significant of PRDX5 localization in organelles needs further investigation (see page 362, col. 1, second paragraph from bottom, in particular). Wang et al does not teach PRDX5 and derivative thereof are effective in treating osteoarthritis as argued. At best, Wang et al teach PRDX5 is detected in human osteoarthritis cartilage at the early stage (less than 48 hours) of inflammatory cytokine release. Wang et al suggest PRDX5 *may* play a protective role in oxidative stress involved in the pathogenesis of oeteoarthritis. Wang et al does not teach treating osteoarthritis, a common process of cartilage degradation in the limbs, by administering PRDX5 to the brain via intracerebral administration, let alone any mouse pup as a model for autoimmune osteoarthritis.

Van Noort *et al* (PTO 892) teach that models of autoimmune diseases depends on numerous factors such as animal strains used, the antigens, the immunization protocol used, especially some protocol for collagen induced arthritis or EAE that result in a single acute episode while others induce chronic relapsing disease (See page 168-169, in particular). Given the time of onset of osteoarthritis, the animal strains used, the antigens and the immunization protocol used in light of the teaching of the specification with respect to osteoarthritis in the literature, it would take undue amount of experimentation to practice the claimed invention.

With respect to the article by Plaisant et al, Plaisant describes the use of PRDX5 in protecting Swiss mice for excitotoxic brain lesions induced by injecting these mice with ibotenate that activates NMDA receptor. Plaisant et al is silent using mouse pups as a model for osteoarthritis. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

7. Claims 4, 6 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any amino acid sequence "having more than 95% *homology*" with the sequence of SEQ ID NO: 2, (2) any pharmaceutical formulation in an orally administrable dosage form, comprising any amino acid sequence "having more than 95% homology" with the sequence of SEQ ID NO: 2, or any

pharmaceutically acceptable salt thereof or any derivative thereof, (3) any amino acid sequence "having more than 95% *homology*" with the sequence of SEQ ID NO: 2 produced in yeast, (4) any pharmaceutical formulation for treating human cerebral palsy, any neurodegenerative conditions associated with oxidative stress related to NMDA receptor mediated excitotoxicity and osteoarthritis, comprising any amino acid sequence "having more than 95% *homology*" with the sequence of SEQ ID NO: 2, any pharmaceutical acceptable salt thereof or any derivative thereof for treating any diseases as set forth in claim 15.

The specification discloses only one human peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 for treating ibotenate induced brain lesions. The specification at page 39 paragraph 136 discloses intracerebral administration of recombinant peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 had no detectable protective effect on other neurotoxic injury or excitotoxic brain lesion induced by S-bromowillardiine. The specification also discloses SEQ ID NOS: 4 and 6, which relate to the rat and mouse PRDX5 sequence, respectively. However, the functions of SEQ ID NO: 4 and 6 have not been described. The specification further discloses peptide consisting of the amino acid sequence selected from the group consisting of the sequence between the glutamic acid in position 14 and the glutamic acid in position 28 of SEQ ID NO: 2, the alanine in position 27 and the leucine in position 37 of SEQ ID NO: 2, the alanine in position 43 and the glutamic acid in position 58 of SEQ ID NO: 2, the glutamic acid in position 57 and the valine in position 70 of SEQ ID NO: 2, the valine in position 81 and the leucine in position 97 of SEQ ID NO: 2, the arginine in position 96 and the leucine in position 112 of SEQ ID NO: 2, the serine in position 119 and the serine in position 130 of SEQ ID NO: 2, and the valine in position 138 and the threonine in position 151 of SEQ ID NO: 2, the glutamic acid in position 14 and the cysteine in position 48, the glutamic acid in position 14 and the glycine in position 39, the leucine in position 37 and the cysteine in position 48 and the threonine in position 151 and the leucine in position 162 for making antibody.

With the exception of the specific polypeptide comprising SEQ ID NO: 2, 4 and 6 or the specific peptide consisting of the amino acid residues mentioned above, there is inadequate written description about the structure, i.e. amino acid sequence associated with function of any derivative of any amino acid sequence merely "having more than 95% homology" with the sequence of SEQ ID NO: 2.

The specification does not adequately describe which amino acids within the full-length sequence of SEQ ID NO: 2 are critical and can or cannot be change by substitution, deletion,

addition and/or combination thereof and whether the variant or derivative still maintains its structure and function, in turn, would useful for treating all neurotoxic injury and/or all excitotoxic injury or osteoarthritis. Since the amino acid sequence having more than 95% homology with the sequence of SEQ ID NO: 2 associated with function is not adequately described, it also follows that any pharmaceutical formulation comprising any undisclosed amino acid sequence is not adequately described.

There is a lack of a written description about which amino acids to be added. The specification does not describe any derivative of SEQ ID NO: 2 such as any fragment from smallest to the largest fragment have any activity in vitro or in vivo, much less for treating any brain lesions caused by any neurotoxic injury or excitotoxic injury, including osteoarthritis.

The specification discloses only human, mouse and rat peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 that is useful for treating ibotenate induced brain lesions and only one reductant DTT, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of homologue that is 95% homologous to SEQ ID NO: 2, derivative thereof, salt thereof to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/17/06 have been fully considered but are not found persuasive.

Applicants' position is that this ground of rejection has been addressed above and the comments made above are incorporated herein by reference. The claims are now limited to SEQ ID NO: 2, the specific subsequences listed in claim 5, and sequences which have 95% homology with SEQ ID NO: 2. SEQ ID NO: 2 and the specific subsequences of claim 5 are described in the present specification. Regarding support for sequences having 95% homology with SEQ ID NO: 2, such support is found in Figure 5, which shows SEQ ID NOS: 4 and 6 having at least 95% homology with SEQ ID NO: 2.

In response, the claims are drawn to any homologue that is 95% identical to SEQ ID NO: 2, any derivative of said homologue for treating any neurotoxic injury or any excitotoxic injury or osteoarthritis.

The specification discloses only one human peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 for treating ibotenate induced brain lesions. The specification at page 39 paragraph 136 discloses intracerebral administration of recombinant peroxiredoxin 5 polypeptide comprising SEQ ID NO: 2 had no detectable protective effect on other neurotoxic injury or excitotoxic brain lesion induced by S-bromowillardiine. The specification also discloses SEQ ID NOS: 4 and 6, which relate to the rat and mouse PRDX5 sequence, respectively. However, the functions of SEQ ID NO: 4 and 6 have not been disclosed.

With the exception of the specific polypeptide comprising SEQ ID NO: 2, 4 and 6 or the specific peptide consisting of the amino acid residues mentioned above, there is inadequate written description about the structure, i.e. amino acid sequence associated with function of any derivative of any amino acid sequence merely "having more than 95% homology" with the sequence of SEQ ID NO: 2.

The specification does not adequately describe which amino acids within the full-length sequence of SEQ ID NO: 2 are critical and can or cannot be change by substitution, deletion, addition and/or combination thereof and whether the variant or derivative still maintains its structure and function, in turn, the derivative would useful for treating all neurotoxic injury, all excitotoxic injury or osteoarthritis. There is a lack of a written description about which amino acids to be added. The specification does not describe any derivative of SEQ ID NO: 2 such as any fragment from smallest to the largest fragment have any activity in vitro or in vivo, much less for treating any brain lesions caused by any neurotoxic injury or excitotoxic injury, including osteoarthritis.

With regard to sequence having 95% homology to SEQ ID NO: 2, the specification discloses only SEQ ID NO: 4 and 6. However, other sequence having 95% homology to SEQ ID NO: 2, and the function of such sequences are not adequately described. Since the structure associated with function of such sequences are not adequately described, it also follows that any pharmaceutical formulation comprising any undisclosed amino acid sequence, any derivative, or any salt thereof is not adequately described.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Knoop et al (J Biol. Chem. 274(43): 30451-30458; Oct 1999; PTO 892).

Knoop *et al* teach an amino acid sequence that having more than 95% homology with the sequence of SEQ ID NO: 2 such as rat antioxidant enzyme of the peroxiredoxin family that has the sequence characterized as shown in SEQ ID NO: 6 (see reference rAOEB166 in Figure 1B starting at residues 52 to 199, in particular). The office interprets the term "characterized" as open-ended to include the reference sequence. The reference sequence rAOEB166 in Figure 1B starting at residues 52 to 199 is 100% identical to the entire length of the sequence of SEQ ID NO: 2. Thus, the reference teachings anticipate the claimed invention.

10. Claims 6, and 14 stands rejected under 35 U.S.C. 102(e) as being anticipated by the US Pat No. 6,197,543 (Filed Oct 1997, PTO 1449).

The '543 patent teaches a derivative of the claimed SEQ ID NO: 2 such as an amino acid sequence such as VMP1 (SEQ ID NO: 1) that has a long stretch of amino acid residues identical to amino acid residues 1 to 162 of claimed SEQ ID NO: 2 (see residues from 53 to 214 of reference SEQ ID NO: 1, in particular). The long stretch of amino acid residues is 100% identical to the claimed amino acid sequence of SEQ ID NO: 2, which is more than 95% homology to the claimed sequence (see reference SEQ ID NO: 1 residues 53 to 202 of the '543 patent, Figure 4A-B from residues 53 to the end, in particular). The reference amino acid sequence is produced in yeast such as *Saccharomyces cerevisiae* (see col. 18, lines 59-63, in particular). The '543 patent further teaches a pharmaceutical formulation for oral administration comprising the reference amino acid sequence or derivative thereof (see col. 22, lines 1-52, col. 23, lines 7-9, in particular) or salt thereof (see col. 29, lines 4-13, in particular) and a pharmaceutically acceptable carrier saline or in combination with other agents such as mannitol, which is an electron donor (see col. 28, lines 7-46, col. 27, lines 47-59, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 7/17/06 have been fully considered but are not found persuasive.

Applicants' position is that the this reference was also cited in the parent application, U.S. Application No. 09/486,167. As set forth in the response of December 18, 2002 in that application, the present application claims priority to Belgium application no. 9700692 (Attachment C), filed August 20, 1997, which predates the filing date of the '543 patent that was filed on October 28, 1997. SEQ ID NO: 2 is entitled to the August 20, 1997 priority date, and thus U.S. 6,197,543 cannot be considered as prior art. Specifically, in Figure 5, Belgian application 9700692 discloses the amino acid sequence of SEQ ID NO: 2 (designated in the text also as SEQ ID NO: 1). On page 5, line 22 to page 6, line 4, Belgian application 9700692 refers to homologues of at least 70%, preferentially more than 85% and even more preferentially over 95% homology with the amino acid sequence of Figure 5. Moreover, Belgian application 9700692 relates to fragments thereof. With respect to claim 5, this ground of rejection is also addressed by amendment, the '543 patent does not disclose the specific subsequences of claim 5.

In response, the rejection of claim 5 is moot since the rejection to said claim has been withdrawn. In response to applicant's argument that the claims entitle to foreign priority date of Belgium application no. 9700692 (Attachment C), filed August 20, 1997, it is noted that the foreign application does not teach SEQ ID NO: 4 and 6, as well as derivative of SEQ ID NO: 2. Therefore, claims 6, 13-15 are entitled to the filing date of 8/20/1998.

11. Claim 5 is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
September 29, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600